REMARKS

Amendments to the Claims

The Applicants respectfully ask the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claims 1-48, 53-61, 63, 67-79, 81-83, 93-94, 96-121, 123-124 and 127-131 were amended, Claims 62, 64-66, 80, 84-92, 95 and 122 were canceled. The Applicants state that all amended claims do not add new subject matter to the present specification.

Independent Claims 1, 12, 18, 44, 48, 54 and 93 recite, in part, conservative BoNT/A amino acid sequence variants where such variants comprises 1-4 conservative amino acid substitutions of a BoNT/A peptide. Support for this embodiment can be found throughout the present specification, *e.g.*, ¶¶ 63-65 at pp. 18-20.

Independent Claims 1, 12, 44, 48 and 123 recite, in part, immunoreactive BoNT/A amino acid sequence fragments where such fragments comprises at least six consecutive amino acids of a BoNT/A peptide. Support for this embodiment can be found throughout the present specification, *e.g.*, ¶¶ 66-68 at pp. 20-21.

Independent Claims 18, 74 and 102 recite, in part, tolerogenic BoNT/A amino acid sequence fragments where such fragments comprises at least six consecutive amino acids of a BoNT/A peptide. Support for this embodiment can be found throughout the present specification, *e.g.*, ¶¶ 92-96 at pp. 31-33.

Independent Claims 31 and 114 recite, in part, immunoreactive BoNT/A amino acid sequence fragments where such fragments comprises at least eight consecutive amino acids of a BoNT/A peptide. Support for this embodiment can be found throughout the present specification, *e.g.*, ¶¶ 104 at pp. 37.

Independent Claim 44 recites, in part, "(d) returning said antibody-depleted blood to said individual." Support for this embodiment can be found throughout the present specification, *e.g.*, ¶¶ 125 at p. 49.

Claim Objections

The Examiner has objected to Claims 1-47 for alleged informalities, indicating that the recited terms in the brackets were not clear and the Markush groups were improperly written. The Applicants have amended these claims to corrected the informalities found and respectfully request withdrawal of the objection against Claims 1-47.

Rejection Pursuant to 35 U.S.C. §112, ¶1 Enablement

The Examiner has rejected Claims 31-43, 84-92 and 114-122 as allegedly lacking enablement under 35 U.S.C. §112, ¶1. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The Examiner contends that the present specification while enabling for methods and compositions for the induction of an immune response, the disclosure does not reasonably provide enablement for the induction of a protective immune response through administering a peptide that is an immunoreactive fragment, conservative variant or a peptide that does not induce a protective immune response there to. The Applicants have amended Claims 31-43 and 114-122 and have canceled Claims 84-92.

The Applicants submit that amended Claims 31-43 and 114-122 are enabled and respectfully request withdrawal of the 35 U.S.C. §112, ¶1 enablement rejection against Claims 31-43 and 114-122.

Rejection Pursuant to 35 U.S.C. §112, ¶2 Indefiniteness

The Examiner has rejected Claims 1-47 and 54-133 as allegedly being indefinite under 35 U.S.C. §112, ¶2. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

With respect to Claims 1-47, the Examiner contends that the phrase "conservative variant" fails to provide adequate structural properties to allow one to identify what is being claimed. The Applicants respectfully submit that amended Claims 1-47 clearly and distinctly claim the

recited peptides and respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefinite rejection for Claims 1-47.

With respect to Claims 54-133, the Examiner contends that the amino acid sequence comprising a peptide of at most 60 amino acids is not clearly or distinctly claimed. The Applicants respectfully submit that amended Claims 54-133 clearly and distinctly claim the recited peptides and respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 2 indefinite rejection for Claims 54-133.

Rejection Pursuant to 35 U.S.C. §102(b), Rosenberg Reference

The Examiner has rejected Claims 1, 5-13, 15, 17, 31-47, 54-62, 64-65, 84-101 and 114-132 as allegedly anticipated under 35 U.S.C. §102(b) by Jana S. Rosenberg et al., *Localization of the Regions on the C-terminal Domain of the Heavy Chain of Botulinum Toxin A Recognized by T Lymphocytes and by Antibodies after Immunization of Mice with Pentavalent Toxoid*, 26(4) Immunol. Invest. 491-504 (1997), hereafter the Rosenberg reference. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

According to *MPEP* §2131, for a reference to anticipated a pending claim, that reference must teach each and every element of the pending claim.

With respect to Claims 1, 5-13, 15 and 17, the Examiner contends that the Rosenberg reference discloses a method that comprises the step of determining the presence or absence of antibodies immunoreactive with a peptide that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claims 1 and 12 recite, in part, "determining the presence or absence in said individual of antibodies immunoreactive with a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1." The Rosenberg reference does not disclose a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1. Claims 5-11, 13, 15 and 17 are dependent on Claims 1 or 12, and as such, are also directed, in part, towards a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1. Thus, the Rosenberg reference does not anticipate the present claims because it does not teach each and every

element. The Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 1, 5-13, 15 and 17.

With respect to Claims 31-43, the Examiner contends that the Rosenberg reference discloses a method of vaccinating an individual with a mixture of two or more BoNT/A peptides and an adjuvant that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 31 recites, in part, "wherein said composition comprises . . . a peptide adjuvant fused to a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1." The Rosenberg reference does not disclose a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1. Claims 32-43 are dependent on Claim 31, and as such, are also directed, in part, towards a vaccine comprising an adjuvant and a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1. Thus, the Rosenberg reference does not anticipate the present claims because it does not teach each and every element. The Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 31-43.

With respect to Claims 44-47, the Examiner contends that the Rosenberg reference discloses a method of removing botulinum toxin blocking antibodies from an individual that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 44 recites, in part, step (d) "returning said antibody-depleted blood to said individual." The Rosenberg reference does not disclose a step where anti-BoNT/A antibody-depleted blood is returned to an individual. Claims 45-47 are dependent on Claim 44, and as such, are also directed, in part, towards returning antibody-depleted blood to the individual. Therefore, the Rosenberg reference cannot anticipate the present claims and the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claim 44-47.

With respect to Claims 54-62 and 64-65, the Examiner contends that the Rosenberg reference discloses a method that comprises the step of determining the presence or

absence of antibodies immunoreactive with a peptide that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 54 recites, in part, "antibodies immunoreact with an amino acid sequence from one of said BoNT/A peptides, said amino acid sequence comprising amino acids 785-803 of SEQ ID NO: 1." The Rosenberg reference does not disclose a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1. Claims 55-62 and 64-65 are dependent on Claim 54, and as such, are also directed, in part, towards a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1. Thus, the Rosenberg reference does not anticipate the present claims because it does not teach each and every element. The Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 54-62 and 64-65.

With respect to Claims 84-92, the Examiner contends that the Rosenberg reference discloses a method of vaccinating an individual with a mixture of two or more BoNT/A peptides and an adjuvant that reads on the present claims. The alleged rejection against Claims 84-92 are immaterial as these claims were canceled.

With respect to Claims 93-101, the Examiner contends that the Rosenberg reference discloses BoNT/A peptides that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 93 recites, in part, BoNT/A peptide of at most 30 amino acids in length and comprising "amino acids 491-509 of SEQ ID NO: 1, amino acids 519-537 of SEQ ID NO: 1, amino acids 533-551 of SEQ ID NO: 1, amino acids 547-565 of SEQ ID NO: 1, amino acids 589-607 of SEQ ID NO: 1, amino acids 631-649 of SEQ ID NO: 1, amino acids 659-677 of SEQ ID NO: 1, amino acids 673-691 of SEQ ID NO: 1, 715-733 of SEQ ID NO: 1, amino acids 743-761 of SEQ ID NO: 1, amino acids 771-789 of SEQ ID NO: 1, amino acids 785-803 of SEQ ID NO: 1, amino acids 813-831 of SEQ ID NO: 1, amino acids 827-845 of SEQ ID NO: 1." The Rosenberg reference does not disclose BoNT/A peptides that comprises any of the specific amino acid sequences recited in the present claims. This reference lists BoNT/A peptides for a different region of the toxin, starting with 855-873 and ending with 1275-1296, see, *e.g.*, Table 1 on p. 497. Claims 94-101 are dependent on

Claim 93, and as such, are also directed, in part, towards the same BoNT/A peptides. Thus, the Rosenberg reference does not anticipate the present claims because it does not teach each and every element. The Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 93-101.

With respect to Claims 114-122, the Examiner contends that the Rosenberg reference discloses vaccine compositions with a mixture of two or more BoNT/A peptides and an adjuvant that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 114 recites, in part, a BoNT/A peptide comprising "an amino acid sequence capable of eliciting an immune response, said amino acid sequence comprising amino acids 785-794 of SEQ ID NO: 1." The Rosenberg reference does not disclose BoNT/A peptides comprising amino acids 785-803 of SEQ ID NO: 1. Claims 115-121 are dependent on Claim 114, and as such, are also directed, in part, towards a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1. Claim 122 was canceled. Thus, the Rosenberg reference does not anticipate the present claims because it does not teach each and every element. The Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 114-122.

With respect to Claims 123, 125-129 and 132, the Examiner contends that the Rosenberg reference discloses a method of preparing antibodies using BoNT/A peptides that read on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 123 recite, in part, a method of preparing an antibody using a BoNT/A peptide where the "BoNT/A peptide comprises an amino acid sequence selected from the group consisting of amino acids 491-509 of SEQ ID NO: 1, amino acids 519-537 of SEQ ID NO: 1, amino acids 533-551 of SEQ ID NO: 1, amino acids 547-565 of SEQ ID NO: 1, amino acids 589-607 of SEQ ID NO: 1, amino acids 631-649 of SEQ ID NO: 1, amino acids 659-677 of SEQ ID NO: 1, amino acids 673-691 of SEQ ID NO: 1, 715-733 of SEQ ID NO: 1, amino acids 743-761 of SEQ ID NO: 1, amino acids 771-789 of SEQ ID NO: 1, amino acids 785-803 of SEQ ID NO: 1, amino acids 813-831 of SEQ ID NO: 1, amino acids 827-

845 of SEQ ID NO: 1." The Rosenberg reference does not disclose BoNT/A peptides that comprises any of the specific amino acid sequences recited in the present claims. This reference lists BoNT/A peptides for a different region of the toxin, starting with 855-873 and ending with 1275-1296, see, *e.g.*, Table 1 on p. 497. Claims 125-129 and 132 are dependent on Claim 123, and as such, are also directed, in part, towards the same BoNT/A peptides. Thus, the Rosenberg reference does not anticipate the present claims because it does not teach each and every element. The Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 123, 125-129 and 132.

Rejection Pursuant to 35 U.S.C. §102(b), Dertzbaugh Reference

The Examiner has rejected Claims 1, 5-13, 15, 17, 31-47, 54-62, 64-65, 84-101 and 114-132 as allegedly anticipated under 35 U.S.C. §102(b) by Mark T. Dertzbaugh and Michael W. West, *Mapping of protective and Cross-reactive domains of the Type A Neurotoxin of Clostridium botulinum*, 14(16) Vaccine 1538-1544 (1996), hereafter the Dertzbaugh reference. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

According to *MPEP* §2131, for a reference to anticipated a pending claim, that reference must teach each and every element of the pending claim. The present independent Claims 1, 31, 44, 54, 84, 85, 93, 114 and 123 all recites, in part, a "BoNT/A peptide." The BoNT/A peptides in the present specification are amino acid fragments of no more than 60 amino acids in length, see, *e.g.*, p. 17, ¶ 61, lines 2-5. The Dertzbaugh reference discloses 10 BoNT/A polypeptides that range from 125-209 amino acids in length, see, *e.g.*, p. 1540, Figure 1. Thus, the Dertzbaugh reference does not anticipate the present claims because it does not teach each and every element. The Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 1, 5-13, 15, 17, 31-47, 54-62, 64-65, 84-101 and 114-132.

Rejection Pursuant to 35 U.S.C. §102(e), Allison Reference

The Examiner has rejected Claims 18-30 as allegedly anticipated under 35 U.S.C. §102(e) by US patent publication 2002/0197278, Anthony Allison, *Covalent Coupling of Botulinum Toxin with Polyethylene Glycol*, (Dec. 26, 2002), hereafter the Allison reference.

Specifically, the Examiner contends that the Allison reference discloses a method that comprises the step of administering a tolerogizing agent together with two or more amino acid sequences of SEQ ID NO: 1 that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

According to *MPEP* §2131, for a reference to anticipated a pending claim, that reference must teach each and every element of the pending claim. The present independent Claim 18 recites, in part, a "BoNT/A peptide conjugated with a tolerogizing agent." Present Claims 19-30 are dependent on Claim 18, and as such, are also directed, in part, towards a BoNT/A peptide conjugated with a tolerogizing agent. The BoNT/A peptides in the present specification are amino acid fragments of no more than 60 amino acids in length, see, *e.g.*, p. 17, ¶ 61, lines 2-5. As such, these peptides are inactive with respect to BoNT/A neurotoxicity and thus not capable of preventing acetylcholine release from nerve terminals.

However, the Allison reference teaches pegylation of the botulinum toxins that retain toxic activity. For example, the Allison reference states in ¶ 10, lines 5-7, "PEG is attached to botulinum toxin at a site, or sites so that it retains the capacity to prevent acetylcholine release from nerve terminals." Likewise, the Allison reference states in ¶ 2, lines 4-5 that the "toxin is modified so as to decrease its side effects and prolong its clinical utility." Thus, the modified toxins disclosed in the Allison reference must retain the ability to bind to a neuron cell receptor, translocate the enzymatic light into the cytoplasm and cleave a SNARE substrate in order to prevent acetylcholine release from nerve terminals. Thus, the Allison reference does not anticipate the present claims because it does not teach each and every element. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(e) rejection for Claims 18-30.

Rejection Pursuant to 35 U.S.C. §102(b), Oshima 1998 Reference

The Examiner has rejected Claims 31-34 as allegedly anticipated under 35 U.S.C. §102(b) by Minako Oshima et al., *Antibodies and T Cells Against Synthetic Peptides of the C-terminal Domain (Hc) of Botulinum Neurotoxin Type A and Their Cross-reaction with Hc*, 60 Immunol. Lett. 7-12 (1998), hereafter the Oshima 98 reference. Specifically, the Examiner contends that the Oshima98 reference discloses a method of vaccinating an individual with

a mixture of two or more BoNT/A peptides and an adjuvant that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 31 recites, in part, "wherein said composition comprises . . . a peptide adjuvant fused to a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1." Claims 32-34 are dependent on Claim 31, and as such, are also directed, in part, towards a vaccine comprising a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1.

The Oshima 98 reference does not disclose a BoNT/A peptide comprising amino acids 785-803 of SEQ ID NO: 1 either alone or in any of the peptide mixtures. This reference lists 16 BoNT/A peptides of 19 amino acids in length and one BoNT/A peptide of 22 amino acids in length all of which correspond portions of amino acids 869-1296 of SEQ ID NO: 1, see, *e.g.*, p. 10, Table2. Thus, the Oshima 98 reference does not anticipate the present claims because it does not teach each and every element. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 31-34.

Rejection Pursuant to 35 U.S.C. §102(b), Oshima 1997 Reference

The Examiner has rejected Claim 44 as allegedly anticipated under 35 U.S.C. §102(b) by Minako Oshima et al., *Immune Recognition of Botulinum Neurotoxin Type A: Regions Recognized by T Cells and Antibodies Against the Protective Hc Fragment (Residues 855-1296) of the Toxin*, 34(14) Mol. Immunol. 1031-1040 (1997), hereafter the Oshima 97 reference. Specifically, the Examiner contends that the Oshima 97 reference discloses a method of removing anti-BoNT/A antibodies from an individual's blood that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 44 recites, in part, step (d) "returning said antibody-depleted blood to said individual." The Oshima 98 reference does not disclose a step where anti-BoNT/A antibody-depleted blood is returned to an individual. Thus, the Oshima 97 reference does not anticipate the present claims because it does not teach each and every element. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claim 44.

Rejection Pursuant to 35 U.S.C. §102(b), Singh Reference

The Examiner has rejected Claims 44-47 as allegedly anticipated under 35 U.S.C. §102(b) by Bal Ram Singh et al., *Immunochemical Characterization of Type A Botulinum Neurotoxin in its Purified and Complexed Forms*, 34(2) Toxicon 267-275 (1996), hereafter the Singh reference. Specifically, the Examiner contends that the Singh reference discloses a method of removing anti-BoNT/A antibodies from an individual's blood that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

First, the present independent Claim 44 recites, in part, step (d) "returning said antibody-depleted blood to said individual." Claims 45-47 are dependent on Claim 44, and as such, are also directed, in part, towards returning the antibody-depleted blood to said individual. The Singh reference does not disclose a step where anti-BoNT/A antibody-depleted blood is returned to an individual.

Second, the present independent Claim 44 recites, in part, step (b) "contacting said blood, or an antibody-containing component thereof, with at least one BoNT/A peptide." Claims 45-47 are dependent on Claim 44, and as such, are also directed, in part, towards contacting said blood, or an antibody-containing component thereof, with at least one BoNT/A peptide. The BoNT/A peptides in the present specification are amino acid fragments of no more than 60 amino acids in length, see, *e.g.*, p. 17, ¶ 61, lines 2-5. The Singh reference does not disclose a step where blood or a blood component is contacted with at least one BoNT/A peptide. This reference discloses a step where the entire 1296 amino acid BoNT/A is used to contact serum, see, *e.g.*, p. 269, ¶ 3 "Affinity purification of antibodies" See also, p. 307, col. 1, ¶ 4, line 5 "Affinity Purification of Anti-botulinum Toxin A Antibody" in Robert A. Ogert et al., *Detection of Clostridium botulinum Toxin A using a Fiber Optic-based Biosensor*, 205 Anal. Biochem. 306-312 (1992) and p. 415, abstract, lines 2-7 in Bibhuti R. DasGupta and Venugopal Sathyamoorthy, *Purification and Amino Acid Composition of Type A Botulinum Neurotoxin*, 22(3) Toxicon 415-424 (1984).

Thus, for these reasons, the Singh reference does not anticipate the present claims because it does not teach each and every element. Therefore, the Singh reference cannot

anticipate the present claims and the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 44-47.

Rejection Pursuant to 35 U.S.C. §102(b), Naumann Reference

The Examiner has rejected Claims 48-50 and 52-53 as allegedly anticipated under 35 U.S.C. §102(b) by Markus Naumann et al., *Depletion of Neutralising Antibodies Resensitises a Secondary Non-responder to Botulinum A Neurotoxin*, 65 J. Neurol Neurosurg. Psychiatry 924-927 (1998), hereafter the Naumann reference. Specifically, the Examiner contends that the Naumann reference discloses a method of determining the level of IgG antibodies immunoreactive with botulinum toxin that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 48 recites, in part, step (a) "determining the level of IgG antibodies immunoreactive with at least one BoNT/A peptide." Claims 49, 50, 52 and 53 are dependent on Claim 48, and as such, are also directed, in part, towards determining the level of IgG antibodies immunoreactive with at least one BoNT/A peptide.

The Naumann reference does not disclose a step where anti-BoNT/A IgG antibodies immunoreact with a BoNT/A peptide. This reference discloses a step where anti-BoNT/A IgG antibodies immunoreact with either staphylococcal protein G, see, *e.g.*, p. 924, col. 2, ¶ 4, lines 1-7; or staphylococcal protein A, see, *e.g.*, p. 925, col. 1, ¶ 4, lines 1-5 and not with BoNT/A peptides. Thus, the Naumann reference does not anticipate the present claims because it does not teach each and every element. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 48-50 and 52-53.

Rejection Pursuant to 35 U.S.C. §102(b), Oshima 1998 Reference

The Examiner has rejected Claims 48 and 51 as allegedly anticipated under 35 U.S.C. §102(b) by Minako Oshima et al., *Antibodies and T Cells Against Synthetic Peptides of the C-terminal Domain (Hc) of Botulinum Neurotoxin Type A and Their Cross-reaction with Hc*, 60 Immunol. Lett. 7-12 (1998), hereafter the Oshima 98 reference. Specifically, the Examiner contends that the Oshima98 reference discloses a method of determining the

level of IgG antibodies immunoreactive with botulinum toxin that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The present independent Claim 48 recites, in part, step (a) "determining the level of IgG antibodies immunoreactive with at least one BoNT/A peptide." Claim 51 is dependent on Claim 48, and as such, is also directed, in part, towards determining the level of IgG antibodies immunoreactive with at least one BoNT/A peptide.

The Oshima 98 reference does not disclose a step where anti-BoNT/A IgG antibodies immunoreact with a BoNT/A peptide. This reference discloses a step where anti-BoNT/A IgG antibodies immunoreact with staphylococcal protein A, see p. 8, col. 2, Section 2.4, lines 18-19 and not with BoNT/A peptides. Thus, the Oshima 98 reference does not anticipate the present claims because it does not teach each and every element. Therefore, the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 48 and 51.

Rejection Pursuant to 35 U.S.C. §102(b), Bavari Reference

The Examiner has rejected Claims 84, 86-100, 114, 116-121, 123, 125-130 and 132 as allegedly anticipated under 35 U.S.C. §102(b) by S. Bavari et al., *Identifying the Principal Protective Antigenic Determinants of Type A Botulinum Neurotoxin*, 16(19) Vaccine 1850-1856 (1998), hereafter the Bavari reference. Specifically, the Examiner contends that the Bavari reference discloses peptide compositions containing an adjuvant an amino acid sequence of 449-473 of SEQ ID NO: 1 that reads on the present claims. The Applicants respectfully ask for reconsideration under 37 C.F.R. §1.111.

The amended Claim 84, 93, 114 and 123 and all claims dependant on these independent claims do not recite a BoNT/A peptide of amino acids 449-473 of SEQ ID NO: 1. Therefore, the Bavari reference cannot anticipate the present claims and the Applicants respectfully request withdrawal of the 35 U.S.C. § 102(b) rejection for Claims 84, 86-100, 114, 116-121, 123, 125-130 and 132.

Rejection Pursuant to 35 U.S.C. §103, Obviousness, Allison in view of Oshima 98

The Examiner has rejected Claims 74-83 and 102-111 as allegedly being obvious under 35 U.S.C. § 103(a) over Anthony Allison, *Covalent Coupling of Botulinum Toxin with Polyethylene Glycol*, US Patent Publication 2002/0197278 (Dec. 26, 2002), hereafter the Allison reference, in view of Minako Oshima et al., *Antibodies and T Cells Against Synthetic Peptides of the C-terminal Domain (Hc) of Botulinum Neurotoxin Type A and Their Cross-reaction with Hc*, 60 Immunol. Lett. 7-12 (1998), hereafter the Oshima 98 reference. Specifically, the Examiner contends that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the compositions and method of the Allison reference with the peptide disclosed in the Oshima 98 reference and produce the invention as presently claimed in Claim 73 and its dependent claims and Claim 102 and its dependent claims.

The Applicant's respectfully submit that the modification of the references in the manner suggested by the Examiner would render the primary reference inoperable for its intended purpose. MPEP § 2143.01 states "If [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."

The Allison reference teaches pegylation of the botulinum toxins and pharmaceutical compositions comprising such modified botulinum toxins that retain toxic activity. For example, the Allison reference states in ¶ 10, lines 5-7, "PEG is attached to botulinum toxin at a site, or sites so that it retains the capacity to prevent acetylcholine release from nerve terminals." Likewise, the Allison reference states in ¶ 2, lines 4-5 that the "toxin is modified so as to decrease its side effects and prolong its clinical utility." Thus, the modified toxins disclosed in the Allison reference must retain the ability to bind to a neuron cell receptor, translocate the enzymatic light into the cytoplasm and cleave a SNARE substrate in order to prevent acetylcholine release from nerve terminals.

The Oshima 98 reference discloses 16 BoNT/A peptides that are 19 amino acids in length and 1 BoNT/A peptide that is 22 amino acids in length, see, *e.g.*, p. 10, Table 2. None of these peptides retain toxic activity. For example, the Oshima reference at p. 8, col 1, ¶ 3, lines 3-5 states that mice were immunized with individual peptides using 50 µg/mouse. As

stated in the present specification, 5.0 pg of BoNT/A is a lethal dose, see, *e.g.*, ¶ 188, lines 4-8. Therefore, a 10,000,000-fold excess of the BoNT/A peptides disclosed in the Oshima 98 reference did not result in lethality.

Thus, to modify the compositions and method of the Allison reference with the peptide disclosed in the Oshima 98 reference as suggested by the Examiner would render the Allison reference inoperable for its intended purpose. Therefore, the Applicants respectfully submit that the Examiner's rejection is unsupported by the art and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 74-83 and 102-111.

Rejection Pursuant to 35 U.S.C. §103, Obviousness, Allison in view of Atassi

The Examiner has rejected Claims 102 and 112-113 as allegedly being obvious under 35 U.S.C. § 103(a) over Anthony Allison, *Covalent Coupling of Botulinum Toxin with Polyethylene Glycol*, US Patent Publication 2002/0197278 (Dec. 26, 2002), hereafter the Allison reference, in view of M Zouhair Atassi and Tetsuo Ashizawa, *PVA or PEG Conjugates of Peptides for Epitope-specific Immunosuppression*, US Patent 6,048,529 (Apr. 11, 2000), hereafter the Atassi reference. Specifically, the Examiner contends that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the compositions and method of the Allison reference with the tolerogizing agents disclosed in the Atassi reference and produce the invention as presently claimed in Claims 102 and 112-113.

The Applicants respectfully submit that a *prima facie* obviousness case fails because the Allison reference and the Atassi reference do not provide motivation, suggestion or teaching that would lead one skilled in the art to specifically make a tolerogizing composition comprising a BoNT/A peptide and a tolerogizing agent as presently claimed.

As stated above, the Allison reference teaches pegylation of the botulinum toxins and pharmaceutical compositions comprising such modified botulinum toxins that retain toxic activity. The Atassi reference teaches additional tolerogizing agents, such as, *e.g.*, monomethoxypolyethylene (mPEG) and polyvinyl alcohol (PVA). Combining these two references would result in botulinum toxins conjugated with either mPEG or PVA that retain

toxic activity. However, the BoNT/A peptides in the present specification are amino acid fragments of no more than 60 amino acids in length, see, *e.g.*, p. 17, ¶ 61, lines 2-5. As such, these peptides are inactive with respect to BoNT/A neurotoxicity and thus not capable of preventing acetylcholine release from nerve terminals. Thus, neither reference teaches, suggests or provides any motivation for the BoNT/A peptides disclosed in the present specification. Therefore, the Applicants respectfully submit that the Examiner's rejection is unsupported by the art and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 102 and 112-113.

Rejection Pursuant to 35 U.S.C. §103, Obviousness, Rosenberg in view of Dertzbaugh

The Examiner has rejected Claim 71 as allegedly being obvious under 35 U.S.C. § 103(a) over Jana S. Rosenberg et al., *Localization of the Regions on the C-terminal Domain of the Heavy Chain of Botulinum Toxin A Recognized by T Lymphocytes and by Antibodies after Immunization of Mice with Pentavalent Toxoid*, 26(4) Immunol. Invest. 491-504 (1997), hereafter the Rosenberg reference, in view of Mark T. Dertzbaugh and Michael W. West, *Mapping of protective and Cross-reactive domains of the Type A Neurotoxin of Clostridium botulinum*, 14(16) Vaccine 1538-1544 (1996), hereafter the Dertzbaugh reference. Specifically, the Examiner contends that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the immunoassay method of the Rosenberg reference to include the ELISA method disclosed in the Dertzbaugh reference and produce the invention as presently claimed in Claim 71.

Claim 71 is a dependant claim to Claim 54. The present independent Claim 54 claims, in part, a BoNT/A peptide having a length of at most 60 amino acids and comprising the amino acids 785-803 of SEQ ID NO: 1, this region being immunoreactive with antibodies. The Rosenberg reference does not disclose a BoNT/A peptide comprising of amino acids 785-803 of SEQ ID NO: 1. The Dertzbaugh reference discloses 10 BoNT/A polypeptides that range from 125-209 amino acids in length, see, *e.g.*, p. 1540, Figure 1. In addition, the Dertzbaugh reference does not provide any teaching, suggestion or motivation to produce a BoNT/A peptide having a length of at most 60 amino acids and comprising the amino acids 785-803 of SEQ ID NO: 1. As this limitation is incorporated by reference to Claim 71, the modification proposed by the Examiner would not be obvious. Therefore, the Applicants

respectfully submit that the Examiner's rejection is unsupported by the art and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claim 71.

Rejection Pursuant to 35 U.S.C. §103, Obviousness, Kubota in view of Harlow

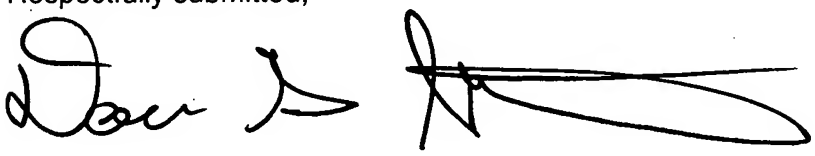
The Examiner has rejected Claims 123 and 133 as allegedly being obvious under 35 U.S.C. § 103(a) over Toru Kubota et al., *Epitope Regions in the Heavy Chain of Clostridium botulinum Type E Neurotoxin Recognized by Monoclonal Antibodies*, 63(4) Applied Environ. Microbiol. 1214-1218 (1997), hereafter the Kubota reference, in view of Harlow and Lane, *Monoclonal Antibodies* in Using Antibodies: A Laboratory Manual New York: Cold Spring Harbor Laboratory Press (1998), hereafter the Harlow reference. Specifically, the Examiner contends that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to obtain monoclonal antibodies as taught by the Kubota to the epitope within the range of amino acids from 655-681 as described and shown to be immunogenetic, in view of the guidance and teaching of the Harlow reference because the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining antibodies as presently claimed in Claims 123 and 133.

The Kubato reference teaches that the monoclonal antibody LE34-6 react with the peptide sequence VIKAIN located at the amino acid positions 663-668 of BoNT/E, see, *e.g.*, p. 1214, abstract, lines 5-6; p. 1217, Table 5 and p. 1217, col. 2, ¶ 4, lines 1-4. Alignments of BoNT/A and BoNT/E indicate that the corresponding region of BoNT/A is peptide sequence TVQTID located at the amino acid positions 691-696, see, *e.g.*, D. Borden Lacy and Raymond C. Stevens, Sequence Homology and Structural Analysis of Clostridial Neurotoxins, 291 J. Mol. Biol. 1091-1104 at p. 1095, Figure 3; and M. Zouhair Atassi and Minako Oshima, Structure, Activity and Immune (T and B Cell) Recognition of Botulinum Neurotoxins 19(3) Crit. Rev. Immunol. 219-260 at p. 224, Figure 1. This epitope recognition sequence is contained in the N18 peptide of the present application, amino acids 687-705 of SEQ ID NO: 1, see, Figure 1A. The N18 peptide is not claimed in either Claim 123 or 133. Therefore, the Applicants respectfully submit that the Examiner's rejection is unsupported by the art and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 123 and 133.

CONCLUSION

For the above reasons the Applicants respectfully submit that the claims are in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. Please use Deposit Account 01-0885 for the payment of the extension fees or any other fees due in connection with the current response.

Respectfully submitted,



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